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NIADDK 1985

Diabetes Mellitus

TRANS-NIH RESEARCH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and
Digestive and Kidney Diseases

DIABETES MELLITUS

Diabetes mellitus affects an estimated 10 million Americans, or about 1 in 20 people in this country. About half of these individuals do not know that they have diabetes. In the past 45 years, there has been an estimated tenfold increase in the prevalence of diabetes; and the number of people with the disease is still growing at a rate of 6 percent per year.

Diabetes can be a devastating condition, both physically and emotionally. Long-term diabetes--even in people who are treated for the disease--can cause serious complications affecting the heart, kidneys, eyes, nerves, and other parts of the body. These complications can be painful, debilitating, and in many cases life-threatening. Diabetes is the fifth leading cause of death by disease in this country.

New information on the cost of diabetes, including loss of income as well as direct medical costs for care of people with the disease, indicates that the economic burden to the country is $14 billion per year. Much of this cost is borne by the government and, ultimately, the taxpayer in the form of programs such as Medicare, Medicaid, and health care services provided by the Veterans Administration. At the same time, the emotional burden and economic cost to the individual with diabetes and his or her family can be overwhelming.

The Impact

The impact of diabetes is well illustrated in the toll taken by diabetic complications:

- Ninety percent of people with insulin-dependent diabetes and many with noninsulin-dependent diabetes experience some manifestation of the long-term complications of the disease.

- Diabetes is the leading cause of blindness among middle-age Americans. About 40 percent of people with diabetes show some degree of diabetic retinopathy. After 15 years, more than 90 percent of people with insulin-dependent diabetes have some degree of diabetic eye disease.

- About 25 percent of people who develop end-stage renal disease, requiring kidney dialysis or transplantation, have diabetes.

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- Serious problems affecting the nervous system afflict as many as 25 percent of all people with diabetes.

- Amputations are at least 15 times more common in people with diabetes than in those without the disease. About half of all nontraumatic amputations done each year are performed on people with diabetes.

- The incidence of congenital malformations in the approximately 10,000 babies born each year to women who develop diabetes before they become pregnant is about four times that in babies of women without diabetes.

- Between 60,000 and 90,000 babies are born each year to women who develop diabetes while they are pregnant. There is a greater risk of excessive size and weight, respiratory distress, jaundice, and stillbirth in these babies.

The Disorder

As scientists look more and more closely at the causes and effects of diabetes, the complexity of the disease becomes more apparent.

Insulin--a hormone made by the pancreas--was thought to be the cure for diabetes when it was first isolated and used successfully to prevent the death of a young boy with acute diabetes in 1922.

Two subsequent discoveries showed that insulin treatment was not a complete cure for diabetes. First, physicians observed that although people with diabetes who were treated with insulin survived for many years, they often suffered from serious "complications" associated with this disease. Second, scientific research identified mechanisms unrelated to production of insulin by the pancreas that could also influence the metabolism of sugar by the body.

Scientists continue to investigate the possible causes of diabetes with the aim of identifying the underlying mechanisms of this disease and developing means of prevention and cure. The second major goal of diabetes research is to understand the mechanism of diabetic complications and, until diabetes can be cured, to prevent and control these associated conditions.

Research

The scientists who first described the effects of insulin on acute diabetes in animals were motivated by a desire to save the lives of people afflicted with this disease. However, the investigative method they used to approach the problem and the techniques that allowed them to isolate

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insulin from the pancreas were not developed in the interest of understanding this particular disease. Scientists seeking a basic understanding of how the body works had previously laid the groundwork for the then unforeseen discovery of insulin.

More recently, research in the fields of genetics, molecular biology, and physical chemistry has provided diabetes researchers with new tools to understand the mechanisms behind the development of diabetes and its complications. An exciting example of this is the research supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) that won Dr. Robert Merrifield of New York's Rockefeller University the 1984 Nobel Prize in chemistry. In the course of basic research on proteins, Dr. Merrifield developed a method of synthesizing peptides--chemicals with the same structure as proteins, but shorter. Application of this method has provided important information on the structure and function of peptides and proteins, of which insulin is only one example. Dr. Merrifield's NIADDK grant, which has been active for almost 30 years, supported the development of this method and his continuing work at the forefront of this research field.

Progress and Promise in Diabetes Research

Using the tools of basic research, scientists have made many important advances in the last few years in the field of diabetes. A conference convened in September 1983 by the congressionally authorized National Diabetes Advisory Board brought together 160 leading diabetes scientists. The participants assessed progress in diabetes research made since the last such conference in 1979 and identified directions for the future. Some notable advances include:

- Insights into the mechanism of inflammatory changes in pancreatic cells in insulin-dependent diabetes and better understanding of the relationship between genetic, immune, and environmental factors in this disease.

- Development of techniques for detecting immune factors in people with newly diagnosed insulin-dependent diabetes and detection of these factors in close relatives of these individuals.

- Identification of many factors that can impair the action of insulin in people with noninsulin-dependent diabetes.

- Complete structural analysis of the human insulin gene and its localization on human chromosome 11.

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- Advances in understanding the control and mechanism of hormone secretion and action.

- Advances in transplantation research that are hastening the day when the first transplant of insulin-producing islet cells will be performed in a human patient.

In the wake of recent years of such extraordinary research productivity, optimism for future progress is now high within the diabetes research community. In this regard, participants at the Second National Conference on Diabetes also made many recommendations regarding areas of particular research need and outstanding scientific opportunity.

Insulin-Dependent Diabetes

Between 300,000 and 500,000 of the 10 million diabetic Americans have the insulin-dependent (IDDM) form of the disease, or type I diabetes. In patients with this type of diabetes, the pancreas produces little or no insulin. The individuals who develop type I diabetes, usually in childhood, characteristically become ill rapidly. Frequent symptoms are great thirst, copious urination, and weight loss. If treatment is not timely, these children may lapse into a coma.

Accumulating evidence testifies that destructive tissue changes occur in these individuals well before symptoms appear. The detection of telltale signs of increased activity by the patient's own immune, or disease-fighting, system indicates that this system, normally protective, has turned against the individual's own pancreatic tissues. One indication that diabetes may be an autoimmune disease is the association between it and other conditions that are thought to involve autoimmunity such as rheumatoid arthritis and certain thyroid and adrenal gland disorders.

Other evidence includes the detection of complexes of antibodies and antigens (substances that stimulate the immune system to produce proteins known as antibodies that fight foreign invaders), the detection of antibodies against insulin-producing pancreatic tissue in the bloodstream of people with the disease, the association of type I diabetes with genetic markers that determine immune responses to foreign tissue, and the presence of certain viral infections around the onset of the disease that may trigger an immune response.

The study of immune processes in diabetes is an active and productive area of research. NIADDK-supported scientists Drs. Stuart Soeldner and George Eisenbarth at the Joslin Clinic in Boston studied a set of twins and a set of triplets in which one of each set of siblings had developed type I diabetes many years earlier. The siblings in the two sets were the offspring of the same fertilized egg (i.e., identical

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or monozygotic). The investigators found that indicators of impending diabetes appeared after several years in the twin of the person with diabetes and one of the triplets of the other person with diabetes. These two individuals eventually became diabetic. The third triplet was still normal at the most recent visit. Studies of identical siblings are important in assessing the influence of genetics on the development of diabetes.

Twins offered another investigator an opportunity to develop a different kind of evidence that an autoimmune response occurs in diabetes. NIADDK grantee Dr. David Sutherland and colleagues at the University of Minnesota General Clinical Research Center, which is supported by the Division of Research Resources (DRR), have been working to develop a safe and effective means of performing pancreas transplants in people with type I diabetes. Recently, Dr. Sutherland transplanted pancreatic segments of four nondiabetic donors to their twins who had long-standing diabetes. The immediate response to the transplant was restoration of normal glucose metabolism without the need for insulin injections. However, within 4 to 8 weeks, three of the twins who were not immunosuppressed by drugs started to show signs of immune attack on the insulin-producing cells in the transplanted segments. The scientists suggest that the original autoimmune response, remembered by the recipient's immune system, recurred with the introduction of the genetically identical pancreatic cells. Azathioprine, an immunosuppressive drug, was administered to the fourth patient; when this report was written, the patient's diabetic symptoms had not returned. However, the patient may need immunosuppressive drugs for the rest of her life in order to retain functioning pancreatic islet tissue. Another strategy that might be used in transplantation, if remembered autoimmune response is a problem, is to select a donor whose tissue matches the recipient closely enough to avoid rejection, but not closely enough so that the autoimmune reaction reappears.

An animal model of type I diabetes, the BB Wistar rat, developed several years ago by NIADDK-supported researchers, is continuing to provide insight into the autoimmune process. Drs. Aldo Rossini, William Chick, and colleagues at the University of Massachusetts at Worcester, where NIADDK funds a Diabetes-Endocrinology Research Center, transferred spleen cells and lymph node cells from animals who had developed diabetes to animals of the same strain who had not developed diabetes. The recipient animals developed diabetes much sooner than they would have normally. The experiment indicates that, in these animals, immunologically active cells can cause the disease. This animal research may lead to the identification of the antigens in the pancreas that trigger the autoimmune response.

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Research is also showing how heredity helps determine susceptibility to the immune destruction of the pancreas. Type I diabetes has been shown to be associated with the presence of certain genetic markers that play a role in shaping the immune response to foreign tissue. The presence of different genetic markers in individuals with diabetes may explain why diabetes does not always develop in the same manner. Drs. Jerome Rotter and David Rimoin at the Harbor-UCLA Medical Center in Torrance, California, suggest that there are two forms of type I diabetes. One form, characterized by autoimmune destruction of insulin-secreting cells, may be associated with one set of genetic markers. This form develops gradually and may occur at any time throughout life. Susceptibility to the other form of type I diabetes may be associated with another set of genetic markers. This form is characterized by the presence of antibodies to insulin, possibly following viral infection. Diabetes develops rapidly in these individuals. If someone would inherit both sets of genetic markers, they might experience a very severe, rapidly developing form of diabetes. Research to confirm or disprove this hypothesis should help determine the roles and relative importance of genetic and environmental influences in the development of type I diabetes.

Noninsulin-Dependent Diabetes

Insulin-dependent diabetes is a devastating disease, and its victims must have insulin injections to survive. However, noninsulin-dependent or type II diabetes affects a much larger number of people, an estimated 9.5 million--approximately one-half of whom are undiagnosed. While type II diabetes in itself may not be life-threatening, as is type I, the complications that develop over time can cause debilitating and life-threatening illness.

Usually people with type II diabetes produce their own insulin. Research on the disease is directed at why sugar metabolism is nevertheless abnormal, who develops type II diabetes, and how it can be treated and prevented.

One major line of research is the investigation of why insulin, though present in people with type II diabetes, is not effective in responding to increases in blood sugar levels. A revolutionary advance in recent years was the determination that hormones act through special receptor sites on the surface of cells. Using molecular biology techniques, the structure of the insulin receptor has been described and research on how insulin acts through the receptor interaction is under way.

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NIADDK-supported studies conducted by Dr. C. Ronald Kahn and colleagues at the Joslin Diabetes Foundation in Boston and NIADDK intramural scientists Drs. Jesse Roth, Phillip Gorden, and Simeon Taylor, and colleagues have reported that conditions of extraordinary degrees of insulin resistance--in which the metabolic effects of insulin are not proportional to the amount present in circulating blood--can be correlated with defects at the cellular level in binding of insulin to its receptor and subsequent metabolic steps.

The NIADDK intramural researchers have made antibodies to the insulin receptor and found that the antibody mimicked the metabolic effects of insulin, even though an intermediate step by which insulin is known to act did not occur. Such immunological techniques can provide information on how metabolism in cells can be altered and whether this metabolic control always occurs in the same manner.

Dr. Michael Czech at the University of Massachusetts in Worcester has been studying receptors of other hormones related to insulin, the insulin-like growth factors, or IGF's. Dr. Czech and colleagues have found that these hormones interact in different ways--for example, in some cases, they will bind to each other's receptors, or one hormone will increase the number of receptors available for another hormone to bind. This research is helping to explain how, at the level of each cell, related and interdependent metabolic processes are coordinated in the action of hormones.

Another important line of research is the development of techniques to predict who will develop type II diabetes. Studies to date indicate that type II diabetes is much more strongly influenced by heredity than type I, but environment and lifestyle also appear to be important.

Scientists at NIADDK's field studies facilities in Phoenix, Arizona, are also studying the development of noninsulin-dependent diabetes and how it can be predicted. These scientists are working with the Pima Indians of Arizona, who have the highest reported rate of noninsulin-dependent diabetes in the world. Research at the Phoenix facility has added to the evidence that family history, obesity, and the presence of glucose intolerance--an inability of the body to dispose of glucose--increase the risk that an individual will develop diabetes.

Of special importance are studies of the natural history of diabetes in the Pima population. NIADDK researcher Dr. Peter Bennett and colleagues have reported that an early step in the development of diabetes in this population is the development of insulin resistance, rather than inability of the pancreas to produce adequate quantities of insulin. In recent studies aimed at the identification of the underlying

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reason for this insulin resistance, the researchers found that the sensitivity with which the intracellular system of glucose transport responds to insulin was decreased in this population. This sensitivity was not restored with insulin treatment and thus may be an underlying early factor in the development of diabetes.

Clinical Aspects of Diabetes

New technology has provided the means for people with diabetes to monitor their disease day-to-day and tailor treatment to their condition. A major multicenter NIADDK-sponsored study, undertaken with the cosponsorship of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Heart, Lung, and Blood Institute (NHLBI), and various other Federal agencies, and with donations of equipment from private companies, is looking at the relationship between "tight" diabetes control and the development of long-term complications. In the spring of 1984, the Diabetes Control and Complications Trial (DCCT) successfully completed recruitment of the target number of volunteers to complete the initial feasibility stage of the trial. In the spring of 1985, the coordinators of the trial expect to have sufficient data to assess whether to expand and continue the trial another 8 to 10 years. Smaller studies of this extremely important question are under way, but a definitive answer from a large-scale controlled study is critical to determine how diabetes can be treated most effectively.

One of the reasons the DCCT is needed is that careful control of diabetes is not easy and in some cases may have its own hazards. For example, people with type I diabetes may suffer from episodes of hypoglycemia, in which the insulin they take to treat their disease lowers their blood sugar too much. This condition can cause loss of consciousness and coma. Because of the possibility that intensive diabetes treatment could increase the risk of hypoglycemia, investigators are looking for ways to predict which people may be most prone to the development of hypoglycemia.

Grant-supported researchers Drs. Philip Cryer and Julio Santiago at Washington University, St. Louis, where NIADDK also supports a Diabetes Research and Training Center, have studied the responses of hormones that counter the effects of insulin and, in so doing, normally avert hypoglycemia. They found that individuals whose production of epinephrine, in response to hypoglycemia, was inadequate were especially at risk. This information may be useful in testing individuals who may be at increased risk for hypoglycemia and taking steps to prevent the condition.

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Cancer of the pancreas is an insidious disease that is rarely detected until it is far advanced. As a result, only about 4 percent of patients live more than 3 years after diagnosis. Although pancreatic cancer currently accounts for only about 3 percent of the new cancer cases and about 5 percent of cancer deaths, its incidence has been rising over the past 25 years for reasons that are still unclear. Little is known about its cause or prevention.

The incidence and death rates for pancreatic cancer are higher in males than in females and higher in the black than in the white population. The annual incidence per 100,000 is 11.9 for white men and 8.0 for white women. Among blacks, the incidence is 17.5 for men and 11.9 for women. Death rates follow a similar pattern: 11.4 for white men, 7.3 for white women, 15.7 for black men, and 10.2 for black women.

Cancer patients who have had their pancreas removed (pancreatectomized) have IDDM as an unavoidable result. They are particularly suitable for the study of diabetes treatment. A team of NCI grantees at Memorial Hospital for Cancer and Allied Diseases in New York City, under the direction of Dr. Daiva R. Bajorunas, is studying the effects of two pancreatic hormones that regulate the storage and use of carbohydrates (sugars). The first hormone, insulin, regulates the uptake of sugar. The second, glucagon, mobilizes the breakdown of a starch stored in the liver for the body to use as sugar. Pancreatectomized patients cannot produce either hormone while diabetic patients have defective insulin and glucagon secretion.

The scientists first studied whether the pancreatectomized patients have an increased sensitivity to insulin. They compared the sensitivity to insulin in three groups: normal volunteers, patients with type II diabetes mellitus, and patients with the surgically induced diabetes resulting from pancreatectomy. Each group was given insulin by infusion and monitored for sensitivity to the insulin. Although the insulin bound to cells to about the same degree in all three groups, cells of the pancreatectomized patients took up less sugar than the other two groups, suggesting a kind of insulin resistance. The scientists concluded that since the cells of the cancer patients apparently have effective binding sites for insulin, some mechanism other than lack of cell sensitivity is apparently responsible for the insulin resistance in the cancer patients.

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The scientists next looked at the role of glucagon in the glucose metabolism. This time they infused pancreatectomized patients with glucagon for 4 hours. Production of blood sugar increased significantly at first but tapered off to about the preinfusion level towards the end. During the infusion period, however, the patients did not metabolize or excrete all the sugar produced, which led to a high blood sugar condition. Results of these findings on the kinetics of insulin and glucagon metabolism will be compared to those obtained in a larger study in progress. The study will include nondiabetic volunteers and patients with diabetes mellitus type I and II.

In followup of a study described in last year's report, NCI grantee Dr. Richard H. Bell of the University of Cincinnati has discovered a relationship in hamsters between the insulin-producing beta cells of the pancreas and the development of pancreatic cancer. His group had been investigating the increased risk of pancreatic cancer associated with diabetes mellitus.

In testing whether diabetes predisposes a person to pancreatic cancer or whether a developing cancer causes the diabetes, Dr. Bell used streptozotocin, a toxin that destroys beta cells, to induce diabetes in Syrian hamsters. He then injected the hamsters with a chemical carcinogen known to cause pancreatic cancer in the animals. As reported in 1983, the streptozotocin protected the hamsters against the development of cancer.

In his recent work, Dr. Bell reversed the order of injections. He injected the hamsters with the carcinogen and then gave them streptozotocin. Unlike the pretreated animals that were protected against the carcinogen, these hamsters did develop cancer. With the beta cells destroyed by streptozotocin in the first study, the carcinogen failed to produce the cancer, but with the beta cells intact at the time of administration in the second study, the carcinogen did produce cancer in the hamsters.

These findings suggest that the beta cells play some role in the development of cancer. Dr. Bell and his colleagues are currently pursuing this lead.

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National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) has an abiding research interest in diabetes because this disease is a potent risk factor for cardiovascular disorders and their complications. Indeed, it is estimated that 25 percent of all diabetics suffer from some form of cardiovascular disease.

Peripheral vascular disease, especially arteriosclerosis affecting blood vessels of the lower extremities, is a common complication of diabetes. In nondiabetics the atherosclerotic obstructions are often confined to relatively short segments of affected arteries. Surgery to remove or bypass these obstructions or the use of balloon-tipped catheters to dilate the blood channel in the narrowed segment are often successful in restoring normal circulation to the threatened limb. However, in diabetics the disease is often more extensive and such procedures are less likely to succeed.

Among diabetics the mortality rate from heart attacks is twice that of the general population, and the prognosis for diabetics who survive the acute episode is appreciably poorer. In the Multicenter Postinfarction Program, a study involving nine participating institutions, NHLBI grantee Dr. Arthur J. Moss and colleagues followed 60 diabetics who survived first heart attacks and compared their prognosis with that of 719 nondiabetic survivors. Over a followup period averaging 19 months, mortality was 25 percent among the diabetic subjects versus only 8 percent among the nondiabetic subjects. All but one of the diabetics who subsequently died succumbed to cardiovascular diseases. With respect to the factors found to influence prognosis (which included cardiac symptoms prior to the attack and frequency of premature ventricular contractions and residual ventricular dysfunction after the acute episode) the diabetic and nondiabetic groups did not differ greatly; but when such differences were statistically accounted for, the diabetic group still exhibited the higher mortality. The investigators conclude that either the diabetic state contributes some unique, but unidentified characteristic that portends a poorer prognosis after heart attacks or else the subsequent progression of coronary atherosclerosis may be accelerated in the diabetic patient.

At the University of Washington (St. Louis) School of Medicine, NHLBI grantee Dr. Allan S. Jaffe and coworkers compared the incidence and severity of congestive heart failure developing after heart attacks between diabetic and nondiabetic patients. Infarct size--the extent of permanent heart-muscle damage resulting from the attack--is usually the major determinant of risk for the subsequent development of congestive heart failure. However, this study showed that, although average infarct size

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was somewhat smaller in diabetic patients than in the nondiabetic control group, the diabetic patients nevertheless had the higher incidence of congestive heart failure (31.2 percent versus 15.7 percent) and also a higher mortality rate from this and related conditions (42 percent versus 32 percent after 2½ years). The incidence of congestive heart failure was especially high among diabetics experiencing their second heart attack (50 percent of the diabetics versus only 16 percent of control subjects).

It is not clear why diabetics who sustain even relatively modest heart-muscle damage remain at such high risk of developing congestive heart failure, a condition that contributes importantly to the excess mortality among diabetics who have sustained heart attacks. The investigators feel that further research is needed to identify other abnormalities in diabetic patients that may contribute to cardiac dysfunction. Such research might well lead to therapeutic measures that could reduce the threat of congestive heart failure and improve long-term survival among diabetic heart attack victims.

Diabetes is frequently associated with blood-lipid abnormalities that may contribute to the increased prevalence of coronary and peripheral atherosclerosis among diabetics. Such abnormalities may be an especially important determinant of risk in diabetic women, according to findings from a study by Dr. Robert Knopp and coworkers at the University of Washington, Seattle. The investigators, whose work was supported by grants from NHLBI and NIADDK, looked at sex differences in blood levels of triglycerides, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol in patients with insulin-dependent or noninsulin-dependent diabetes, comparing these values with those found in nondiabetic control subjects. They found that regardless of the type of diabetes or type of treatment regimen, diabetic women exhibited consistently higher median levels of triglycerides and LDL cholesterol than did diabetic men or control subjects. Both of these lipid fractions are thought to be atherogenic. Conversely, diabetic women had lower median levels of HDL cholesterol than did diabetic men or control subjects. This fraction appears to be protective against atherosclerosis and the higher the HDL cholesterol level the better.

The investigators conclude that diabetes has a greater adverse effect on blood lipids in diabetic women than in diabetic men. Measures to reverse these effects toward the goal of reducing risk of atherosclerotic vascular disease deserve high priority in the treatment of the female diabetic.

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National Institute of Dental Research

The National Institute of Dental Research (NIDR) conducts and supports research in diabetes because of the oral complications associated with this disease. These complications include greater susceptibility to periodontal diseases and oral fungal infections, increased loss of bone in toothless individuals, reduced salivation, and diminished senses of taste and smell. NIDR extramural research has focused on periodontal disease, whereas intramural efforts have dealt with the basic causes of diabetes.

NIDR intramural scientists have continued to study the basic causes of diabetes. Under the direction of Dr. Abner L. Notkins, intramural scientists are examining the role of viruses and immunity in human and animal models of diabetes.

These investigators believe that diabetes involves an immunological "mistake" in which the body produces antibodies against itself. Normally, immune responses destroy invading bacteria, viruses, and tumors--foreign substances. Researchers know that many patients with type I diabetes have autoantibodies in their blood, and they believe that these autoantibodies can attack the beta cells and possibly produce diabetes.

Scientists know little about what triggers the production of these autoantibodies, but viruses have been suspected as one of the possible causes.

Recently, Dr. Notkins and his colleagues successfully produced mouse and human monoclonal autoantibodies in the laboratory. The availability of large quantities of autoantibodies should enable them to identify the antigens these antibodies recognize, the role they play in autoimmune diseases, and whether different individuals with the same disease develop autoantibodies against the same molecules.

Using these monoclonal autoantibodies, the scientists have begun to extract the specific antigens with which these antibodies react. Such information will be invaluable in learning not only how these diseases are switched on, but also how they can be turned off.

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National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) serves as the Federal Government's focal point for research on diabetic neuropathy. A serious neurological complication, diabetic neuropathy affects about 10 percent of the more than 10 million diabetics in the United States. Symptoms may include burning sensations, numbness, weakness, and paralysis in the hands and feet. According to some scientists, these symptoms are caused by the effect of diabetes on nerve-cell metabolism. Other investigators, however, believe that the symptoms result indirectly from blood vessel damage caused by diabetes.

In an NINCDS-supported clinical research program project at the Mayo Clinic in Minnesota, Dr. Peter Dyck and colleagues are studying tissues from the peripheral nerves of patients who died with insulin-dependent diabetes mellitus and neuropathies. (Peripheral nerves are those that course through the entire body, connecting the spinal cord to muscles, skin, blood vessels, and other parts of the body.) Dr. Dyck's team is comparing these tissues with those from a control population of nondiabetics who died from other disorders. These examinations suggest that the nerve damage in diabetics occurs at specific sites and is not widespread, and thus probably does not result from the general metabolic problems associated with diabetes.

Other findings from this research suggest a relationship between neuropathy and the changes around the nerve cell that result from decreased blood flow. The team compared leg nerves of diabetic patients, both with and without neuropathy, with those of control patients. The neuropathy patients proved to have by far the greatest number of tiny blood vessels so constricted or closed that they could not serve as a conduit for blood. This observation suggests decreased blood flow around the nerves in diabetic neuropathy. This is supported by the team's finding that in rats with experimentally induced diabetic neuropathy, decreased blood flow was associated with abnormal transmission of nerve cell impulses.

In a continuing project, Dr. Dyck and his colleagues are studying how closely monitored blood glucose control affects peripheral nerve function. The research team is using a computer to measure nerve function and determine the degree of nerve impairment. They have found improved nerve conduction after 8 months in diabetic patients whose blood glucose levels were closely controlled.

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Dr. Henry Powell, an NINCDS grantee at the University of California at San Diego, is using rats with drug-induced diabetes as a model of the human disorder. He and his colleagues have discovered evidence that supports the theory that high levels of fluid outside the nerve cell are somehow related to the decreased blood flow seen in the induced neuropathy.

NINCDS-supported studies on stroke have identified diabetes as a main risk factor, and are yielding new information on this relationship. Scientists have developed a theory that abnormally high blood glucose concentrations during the early stages of acute stroke will extend the area of brain damage, and that reducing glucose concentrations in the blood and brain will lessen the extent of damage. Based on this theory, NINCDS grantee Dr. William Pulsinelli and colleagues at Cornell University Medical College, New York, are investigating the safety of using insulin injections to lower the blood glucose concentration of patients with acute stroke rapidly. Once the scientists have established the safety of this approach, they will determine the effectiveness of intensive insulin treatment for reducing brain damage associated with stroke.

Measurement of chemosensory abilities--taste and smell--provides opportunities for noninvasive detection of diseases such as noninsulin-dependent diabetes. Dr. James Snow and colleagues at an NINCDS-supported smell and taste clinical research center at the University of Pennsylvania are studying sensitivity to glucose and fructose (another type of sugar found in food) among relatives of diabetics who are not insulin-dependent. Some of these family members have shown a decrease in perceived sensitivity to the taste of glucose compared to fructose. These results indicate that abnormal sensitivity to glucose may be a genetic characteristic that is both a sign of and a contributor to noninsulin-dependent diabetes.

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National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) has a special concern for the medical problems confronting diabetics. Infections are both more frequent and more serious in diabetics, as a group, than in the general population. The Institute's basic immunology research is furthering the understanding of the immunologic processes and how the immune response of the diabetic differs from that of the normal individual.

NIAID grantee Dr. Michael A. B. Oldstone and his colleagues at Scripps Clinic and Research Foundation in La Jolla, California, are conducting research in mice on a possible viral connection to diabetes. They have demonstrated that a virus that does not cause structural injury can disturb endocrine functions by disrupting the synthesis of a hormone needed for growth and glucose regulation. To do so, the virus replicates in specialized cells making that hormone, thereby altering hormone output.

This conclusion was based on observations that several different mouse strains, when infected at birth with lymphocytic choriomeningitis virus (LCMV)-Armstrong strain, had clear-cut developmental retardation manifested by diminished weight gain and growth. The pituitaries removed from the mice by the scientists were structurally normal, but the levels of growth hormone in the pituitaries of infected mice were significantly lower than in those of uninfected age and sex matched controls. The two major activities of growth hormone are the regulation of growth and glucose metabolism. Accordingly, the infected mice had significant reductions in growth and became defective in glucose metabolism.

The role of growth hormone deficiency in the mice infected with virus was further demonstrated when they received transplants of cloned growth hormone-producing cells. These transplants completely reversed the severe hyperglycemia and corrected both weight and length to normal standards.

Most recently, Dr. Oldstone and fellow researchers have noted that a virus could persist in beta cells of the islets of Langerhans (located in the pancreas) without causing any structural abnormalities. Yet, such persistently infected mice showed chemical manifestations similar to type II diabetes.

Thus, these studies are contributing significantly to the vital knowledge being developed on viral infections as a possible cause of diabetes.

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A potentially fatal fungal infection, mucormycosis, is increasingly being seen in patients with uncontrolled diabetes, although the reason for this unusual predisposition is as yet unknown. Mucormycosis is caused by the inhalation of fungal spores released into the environment by decaying vegetation. The fungus can attack rapidly and with great intensity, affecting the nose, the paranasal sinuses, and ultimately the brain. This disease is seen most often in those with serious underlying health problems.

Because of the serious danger to diabetics from mucormycosis, NIAID grantee Dr. Alayn Waldorf and her colleagues at University Hospital in Boston are conducting vital research on this disease in an effort to gain an understanding of not only why it is increasing in frequency, but also why it has a propensity for striking diabetics.

These investigators have developed a mouse model system that closely resembles human infection. This model of experimentally induced diabetes provides a system for examining host immune factors affecting the cause of mucormycosis and for detailing specific defects that predispose diabetic subjects to this deadly disease.

Although it is too early to provide conclusive information, the scientists are optimistic that their studies will contribute to an understanding of the cause of mucormycosis and help answer the most important questions concerning antimicrobial defenses in general. Only through basic research can answers be found to prevent needless suffering and death from this and other life-threatening infections in the diabetic.

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National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training that provide the foundation for a better understanding of fundamental life processes. This research supplies new knowledge, theories, and concepts for the disease-targeted programs of other NIH Institutes.

One of NIGMS' major programs supports basic research on genetics. Much of this work has relevance to diabetes, a disorder in which heredity plays a part. Although we know that diabetes is a "multifactorial" disorder--that is, more than one defective gene and probably environmental influences as well are involved--we do not know the relative contributions of each variable to the disease's development. Identifying the complex causes of multifactorial diseases would be an important step toward understanding them.

NIGMS is supporting a number of grants designed to develop statistical models and computer programs that will help sort out the roles of heredity and environmental factors in diabetes and other multifactorial disorders. This work will help determine what specific kinds of information are needed about family history and environmental variables in order to predict an individual's likelihood of developing a multifactorial disease like diabetes. Better prediction may lead to earlier treatment and, in some cases, prevention.

One grantee working in this area, Dr. Samuel Karlin of Stanford University in Stanford, California, is developing complex mathematical theories that help him evaluate a great many possible risk factors for disease. His work may advance efforts to understand multifactorial disorders by identifying how cultural or behavioral patterns interact with genetic factors to cause disease.

Another grantee, Dr. Jean MacCluer of the Southwest Foundation for Research and Education in San Antonio, Texas, is developing methods to evaluate many computer programs used to analyze genetic data on complex disorders. She will identify the strengths and weaknesses in various programs and help scientists design more effective systems.

To facilitate research on diabetes and other genetic disorders, NIGMS supports the Human Genetic Mutant Cell Repository at the Institute of Medical Research in Camden, New Jersey. This repository establishes and stores cultured cell lines collected from patients with well-characterized genetic disorders as well as from members of their families and from normal volunteers. These cells are provided to requesting

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scientists at modest charge, thus enabling them to study the cellular aspects of many genetic disorders without first having to locate a cell donor. At present, the repository maintains 123 lines of cells from diabetic patients and their families.

Defective insulin binding and processing are probably involved in some types of diabetes. At the University of Arizona in Tucson, grantee Dr. Nobuyoshi Shimizu has developed mutant cell lines that are defective in insulin binding. He is now characterizing the biochemistry of these cells and will use them to help map the location of the genes involved in the binding, internalization, and processing of insulin. Knowledge gained from these studies will contribute to our understanding of the hormonal regulation of cells and may help explain one of the mechanisms leading to the development of diabetes.

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National Institute of Child Health and Human Development

Untreated diabetes mellitus in a pregnant mother is incompatible with the health of both mother and child. As treatment of diabetes has improved, pregnancy outcome has improved, but diabetes in pregnancy still constitutes a major health problem. Presently, maternal mortality is similar for both diabetic and nondiabetic women, but there are more complications of pregnancy among diabetic women.

With careful medical supervision, perinatal (the period shortly before and after birth) mortality in diabetic pregnancy has been reduced to approximately 4 percent, still higher than for the general population. There is an increased incidence of congenital anomalies, macrosomia (large body size), late intrauterine death, and respiratory distress syndrome in the newborn in diabetic pregnancies.

Pregnancy itself has a diabetes-generating effect. Some women develop temporary abnormalities of carbohydrate metabolism--a hallmark of diabetes--termed gestational diabetes; others may develop true diabetes during pregnancy. In either case, the intrauterine environment is unfavorable for the developing fetus. The adverse effects on the fetus correlate directly with the severity of the maternal disease.

The National Institute of Child Health and Human Development (NICHD) supports four Perinatal Emphasis Research Centers (PERC's) in the area of diabetes.

Animal models (rhesus monkey, rat, and lamb) have been developed, which manifest chronic in utero hyperinsulinemia--greater-than-normal insulin blood levels--resulting in fetal overgrowth (similar to human fetal macrosomia). NICHD grantees Drs. Pierre Galletti, William Oh, and Robert Schwartz at Brown University, Providence, Rhode Island, have shown that insulin appears to play a predominant role in controlling human and subhuman primate fetal growth. Measurements of fetal somatomedin--a growth-mediating hormone--in humans support this concept as no differences were found between the levels in insulin-dependent diabetics and in nondiabetic controls. Fetal macrosomia was also produced in rats by injecting insulin directly into the fetus, which indicates that insulin is a lipogenic or fat-generating hormone.

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Another approach to produce a fetal hyperinsulinemic state is to induce diabetes in the pregnant rat by the administration in early gestation of streptozotocin (a drug used in experimental conditions, which destroys insulin-producing pancreatic islets causing diabetes). NICHD-supported investigators Drs. Robert Greenberg and John Johnson at the University of New Mexico, Albuquerque, showed that even though the maternal diabetes is corrected with insulin therapy, the fetal abnormalities are only partially rectified. In addition, they demonstrated that the observed increase in placental size is related to maternal glucose levels rather than to fetal insulin concentrations.

These same investigators have also successfully established and standardized a whole rat embryo culture system, which will provide the means to study events occurring in a high glucose environment and characterize their effect on growth and maturation. Studies using islets from the pancreas of fetal rats have shown that insulin release is greater in islets obtained from normal fetuses than in those whose mothers were treated with streptozotocin.

Studies conducted by NICHD grantee Dr. Norbert Freinkel at Northwestern University in Chicago have compared energy metabolism in women with normal carbohydrate metabolism who are in the third trimester of their first pregnancy with that in the well-controlled pregnant insulin-dependent diabetic. These studies are providing evidence for the desirability of multiple feedings in the management of the pregnant diabetic and highlight the potential harm of even mild caloric restriction. Pregnant women who have a diagnosis of gestational diabetes mellitus (GDM) early in pregnancy are more likely to have postpartum glucose intolerance, indicating that the time of detection of GDM may have prognostic significance.

Dr. Philip Eaton at the PERC at the University of New Mexico, Albuquerque, and colleagues are progressing in the development of an external programmable microelectronic control system to regulate the infusion of insulin in ambulatory patients. Eventually this control system will be used together with an implantable pump and reservoir for insulin administration. These technical advances will facilitate the treatment of insulin-dependent diabetic pregnant women and children.

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Of the 10 million people in the United States who have diabetes, approximately 4 million have at least mild signs of diabetic retinopathy. This potentially blinding eye disease affects the retina, the light-sensing tissue that lines the inside of the eye. An estimated 600,000 Americans are now in serious danger of visual impairment because of diabetic retinopathy; 300,000 have already suffered severe vision loss, and 32,000 of these are legally blind. In fact, diabetic retinopathy is the leading cause of new cases of blindness among middle-age people in this country.

To reduce the toll of visual loss from diabetes and give people with this disorder a better chance to enjoy a lifetime of good visual health, the National Eye Institute (NEI) supports and conducts a wide range of research projects aimed at obtaining new information relevant to the diagnosis, treatment, and prevention of diabetes-related eye problems. Some of these projects are clinical trials that evaluate new methods or strategies for protecting the eye from diabetes-related visual loss. Others are laboratory studies that delve into the basic mechanisms by which diabetes exerts its harmful effects on the retina and other tissues. This laboratory research is a fertile source of new clues about possible preventive or therapeutic measures that may later be evaluated in a clinical setting.

A major new clinical study that had its origins in basic research is the Sorbinil Retinopathy Trial (SRT),* a nationwide multicenter study that is supported by the pharmaceutical firm Pfizer, Inc., in cooperation with the NEI clinical facility and 11 other participating centers across the country. The study will determine whether sorbinil--a new investigational drug that belongs to a class of compounds called aldose reductase inhibitors--can prevent or slow down the development of diabetic retinopathy in people who do not yet show serious signs of the eye disorder but are known to be at high risk for such problems.

If sorbinil or any other aldose reductase inhibitor is found effective in protecting the human retina against diabetes-induced damage, this finding will represent the clinical pay-off for a decade of laboratory research conducted at NEI by Dr. Jin Kinoshita and his colleagues. Years ago they discovered that

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* The SRT chairman is Dr. Matthew Davis of the University of Wisconsin at Madison. Clinics participating in the SRT are located in: Los Angeles, California; Louisville, Kentucky; New Orleans, Louisiana; Baltimore and Bethesda, Maryland; Boston, Massachusetts; Portland, Oregon; Houston, Texas; Salt Lake City, Utah; and Madison and Marshfield, Wisconsin.

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the "sugar cataracts" which develop in diabetic rodents arise through the action of an enzyme called aldose reductase. This enzyme, which is normally present in the lens and many other tissues of the body, apparently causes no harm except in the presence of abnormally high levels of blood sugar--such as those that exist in diabetes and in galactosemia (another metabolic disorder that can be produced in laboratory animals). When excess sugar is present, aldose reductase converts it into compounds that can bring about cellular change. Dr. Kinoshita and his coworkers showed that it was possible to prevent diabetes-induced tissue damage in rodents by using aldose reductase inhibitors to block the enzyme's activity.

More recently, NEI grantees Dr. Robert Frank of Wayne State University in Detroit, Michigan, Dr. Ronald Engerman of the University of Wisconsin at Madison, and their coworkers have grown retinal pericytes (the cells that encircle the outside of the retina's blood vessels) in cell culture in the presence of various simple sugars. These investigators have demonstrated that when sugar levels are excessively high, the pericytes accumulate harmful substances that are produced through the action of aldose reductase. This suggests that the enzyme is involved in some of the earliest retinal changes associated with diabetes, and further strengthens the hope that aldose reductase inhibitors will be of value in protecting the retina from diabetes-related disease.

NEI also supports many other projects dealing with the ocular complications of diabetes. For example, NEI-supported scientists are attempting to develop better animal models of diabetic retinopathy. The aim is to find a model in which the animals develop the full sequence of retinal changes that are observed in human diabetic retinopathy, and do so within a short enough period of time to make them convenient subjects for future studies on the disease. Also, NEI grantees are continuing to study cultured cells from the retina to learn more about the cellular basis for the harmful effects of diabetes. It is expected that these and other basic studies on the ocular complications of diabetes will lay the groundwork for future clinical advances in this area.

In addition to these studies devoted to prevention of diabetic retinopathy, NEI continues to support clinical trials aimed at evaluating treatment strategies for people who already have this eye disease. In the largest of these trials,

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the Early Treatment Diabetic Retinopathy Study (ETDRS),* a major goal is to test the effectiveness of argon laser treatment in people whose diabetic retinopathy is only moderately advanced; these are people in whom the disease has produced noticeable retinal abnormalities but has not progressed far enough to pose a serious and immediate risk of blindness. Thanks to an earlier NEI study, it is now known that argon laser treatment can reduce the risk of blindness by 60 percent in people with severe diabetic retinopathy. The current study will determine whether this treatment can benefit the much larger group of diabetics who have milder eye disease. Also, the study will evaluate aspirin treatment as a possible means of slowing the progression of diabetic retinopathy in these patients. Included in the study will be patients with macular edema, a diabetes-related retinal problem that causes blurring of vision. This year the ETDRS came close to reaching its recruitment goal of 4,000 patients. As of mid-July, 3,662 patients had been enrolled and assigned to treatment. Recruitment will end in March 1985.

Another NEI-sponsored study is evaluating a different laser--the krypton laser--to determine whether it offers any advantages over the more widely used argon laser for the treatment of some of the retinal abnormalities that often occur in people with advanced diabetic retinopathy.**

By supporting this large and multifaceted research program on the prevention and treatment of the ocular complications of diabetes, the National Eye Institute takes advantage of scientific opportunities to protect the sight of people with this disease and thus reduce the nationwide toll of blinding disease.

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* The ETDRS is supported by NEI research contracts. Its chairman is Dr. Lloyd Aiello of the Joslin Diabetes Foundation in Boston, Massachusetts. Clinics participating in the ETDRS are located in Los Angeles, Menlo Park, and San Francisco, California; Miami, Florida; Chicago and Harvey, Illinois; New Orleans, Louisiana; Baltimore, Maryland; Boston, Massachusetts; Detroit and Royal Oak, Michigan; Minneapolis, Minnesota; Albany, New York; Portland, Oregon; Philadelphia, Pennsylvania; San Juan, Puerto Rico; Houston, Texas; Salt Lake City, Utah; Seattle, Washington; and Madison and Milwaukee, Wisconsin.

**This Krypton-Argon Regression of Neovascularization Study (KARNS) is directed by Dr. Richard Mowery of NEI. Clinics currently participating in KARNS are located in: Los Angeles, California; Chicago, Illinois; Baltimore, Maryland; Beachwood, Ohio; Oklahoma City, Oklahoma; Philadelphia, Pennsylvania; Madison, Wisconsin; and Cheyenne, Wyoming. Additional clinics are expected to join the study within the next year.

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Pathological findings in insulin-dependent diabetes mellitus include a substantial decrease in the absolute number of insulin-secreting pancreatic beta cells. In noninsulin-dependent diabetes a frequent finding is an impairment in beta cell function. There is evidence that in some forms of diabetes environmental factors, among them chemicals such as N-nitroso compounds, play a role in the depletion of insulin-secreting pancreatic tissue. The effect of these compounds on pancreatic cells is being studied in tissue culture. It has been shown previously that streptozotocin, a nitroso compound, causes diabetes. Dr. Glen Wilson and colleagues at the University of South Alabama College of Medicine in Mobile have shown that closely related compounds also can initiate diabetes. Their studies are significant for human health in two ways. First, they should help in the identification of new and existing chemicals that cause diabetes. Second, they will be important in developing strategies to prevent the diabetogenic effects of chemical and other pollutants in humans.

Dr. Brooke Mossman and his colleagues at the University of Vermont College of Medicine in Burlington are studying how N-nitroso compounds in the environment damage insulin-secreting cells of the pancreas. The two chemicals chosen for study are streptozotocin and chlorozotocin. Chlorozotocin is a cancer chemotherapeutic agent. Both are members of a broad class of chemicals found throughout the environment, and are being investigated using in vivo and in vitro techniques. Experiments to date indicate that diabetogenic N-nitroso compounds act on DNA in a variety of ways; however, the interaction of the glucose (sugar) part of these compounds with the plasma membrane of cells appears to be a common event in the course of cell injury. This study could provide insight into the initiation of diabetes in humans.

One of the consequences of diabetes is a change in the way the liver metabolizes environmental compounds. Dr. David Cook and his associates at the University of Nebraska Medical Center in Omaha have begun a new study relating this altered hepatic metabolism to the susceptibility of diabetics to chemical toxicants and carcinogens encountered in the environment. An understanding of these relationships is important to those who oversee the care of diabetic patients and individuals interested in the hormonal regulation of biochemical processes involved in metabolism.

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National Institute on Aging

The National Institute on Aging (NIA) supports research on aspects of diabetes that relate to aging and the elderly. Over 85 percent of all cases of diabetes are the noninsulin-dependent form (type II), which affects older people.

Because of the nature of the disease process, scientists have suspected that diabetes can affect mental functioning in older patients. However, there has been a surprising lack of information on this subject. Investigators supported by NIA have completed a study that documents, for the first time, that cognitive abilities tend to decline in older people with type II diabetes.

Drs. Lawrence C. Perlmuter and David M. Nathan and their associates at the Veterans Administration Outpatient Clinic and Massachusetts General Hospital in Boston gave a variety of tests to male and female diabetics ages 55 to 74 and to healthy people the same age who served as controls. They found that those with the disease got significantly lower scores. The diabetics and controls had similar educations, vocabulary skills, reaction times, and other factors that influence success in taking tests.

Two different types of memory tests were given. The first type, the digit span test, measures short-term memory. In the initial phases of this test, diabetics performed as well as controls. However, as the tasks became more difficult, those with the disorder had increasingly poorer scores. The second type of test, the serial learning task, requires the subject to store information and then retrieve it later. Diabetic individuals consistently performed at lower levels than healthy people the same age.

The results of the study suggest that the diabetic's ability to store information for both short and long periods, and then recall it, is diminished either because of the disease and its associated treatment, or because of some underlying factor producing both the disease and the memory deficit. Even the most capable of the diabetic learners performed more poorly than the comparable nondiabetics.

In the course of normal aging, the ability to recall recently learned information tends to decline. But this study showed that diabetes or factors associated with the disease accelerate the decline. At every age, nondiabetics performed better on the tests than did those with the disease. The mean cognitive score for the oldest controls was higher than that of the youngest diabetics. The diabetics who had the greatest degree of peripheral neuropathy (nerve damage) performed the worst on tests. Evidence was also found that poor control of the disease was associated with low test performance.

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Dr. Perlmuter believes that memory impairment in older diabetics could be serious enough to interfere with their compliance with doctors' instructions. He suggests that physicians who treat older diabetics may need to alter their treatment strategies to be sure these patients receive proper care.

Another research group supported by NIA has completed two studies showing that weight control and exercise improve insulin action. These findings have important implications for normal individuals as well as diabetics, since glucose tolerance tends to decrease in everyone with age.

In the first study, Dr. Gerald M. Reaven and his associates at the Stanford University School of Medicine and Veterans Administration Medical Center in Stanford, California, found that 12 overweight patients over 65 years of age who had noninsulin-dependent diabetes improved dramatically after losing an average of 9 kilograms (about 20 pounds). Before the weight loss program, all the patients needed insulin injections to control their disease. But after they lost the excess weight, control could be achieved with an oral drug. Fasting blood glucose levels, a measure of diabetic control, were much better than they had been during insulin treatment. These successes were achieved despite the fact that the patients lost only a moderate amount of weight.

The second study evaluated the effect of different levels of physical activity on insulin action in healthy men between 60 and 75 years of age. None of the 20 participants was overweight and all had normal glucose tolerance. Thirteen of the men were active but had not exercised regularly; the remaining seven had followed a regular program of running, swimming, or bicycling for at least 45 minutes three or more times a week. The scientists measured insulin-stimulated glucose disposal (a measure of insulin action), maximal O_2 consumption (aerobic capacity), and other factors in the two groups and compared them. Insulin action was significantly increased in the participants who exercised regularly. Furthermore, maximal aerobic capacity was directly related to insulin action. Although insulin action is known to decrease with advancing age, this varies widely among individuals. Dr. Reaven's study suggests that differences in physical activity may help explain the variations, with those who exercise maintaining better glucose tolerance.

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Division of Research Resources

Diabetes is being studied extensively at 60 of the 75 General Clinical Research Centers (GCRC's) supported by the Division of Research Resources in major U.S. medical centers. Each year scientists conduct more than 3,000 research studies in GCRC's, with more than 80 percent of the extramural inpatient research funded by NIH taking place in these centers. In addition, extensive outpatient research is also being done.

Much of the diabetes research has centered on ways to adequately control the disease and associated complications. Seventeen GCRC's are participating in a clinical trial described earlier in this report which seeks to determine if precise blood sugar control for up to 10 years can reduce the incidence and severity of complications arising from insulin-dependent diabetes.

One of the earliest complications of insulin-dependent diabetes can be reversed by the use of the insulin infusion pump, according to researchers at the University of Texas Health Science Center in Dallas.

A study at the Dallas GCRC by NIADDK grantee Dr. Philip Raskin and colleagues demonstrated that thickening of the capillary basement membrane in skeletal muscle is reduced after long-term control of glucose levels with an insulin pump. The basement membrane, which is located on the outside of capillary blood vessels, is characteristically thickened in the eye, kidney, and skeletal muscle of diabetics.

The scientists measured the widths of the capillary basement membranes present in skeletal muscle biopsies removed from two groups of diabetic subjects and one group of nondiabetic volunteers. The membrane widths were measured before, during, and after the study. One group of diabetics received constant infusions of insulin from an insulin pump during the study period, whereas the other diabetic subjects followed the conventional regimen of insulin injections twice daily. A third group of nondiabetic subjects served as a control.

The width of the capillary basement membrane decreased progressively among the diabetics who received continuous insulin, and after 2 years the width did not differ significantly from the membrane width of the nondiabetic subjects. Measurements of the membrane width before and after the study were identical in the subjects receiving insulin injections. The membrane widths of these diabetic subjects were wider than those in the nondiabetic subjects.

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An elevated growth hormone level may be one factor that causes poor control of diabetes and diabetes complications. In a study conducted at both the adult GCRC and the children's GCRC of Yale University in New Haven, Connecticut, excess growth hormone was administered hourly to 14 patients whose diabetes was under optimal control. Within 8 hours after the first administration of the hormone the blood sugar level in all subjects had risen significantly. Blood concentrations of other major metabolic fuels also increased. These changes, which persisted until growth hormone administration was discontinued, reflect deteriorating control of the disease.

The data indicate that growth hormone may be a factor in a vicious cycle in diabetes, according to NIADDK grantee Dr. Martin Press, who conducted the study in collaboration with Dr. William Tamborlane and Dr. Robert Sherwin. Growth hormone may stimulate glucose production by the liver, thus worsening diabetic control and causing a further rise in growth hormone concentrations.

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Outlook

Productivity in diabetes research is challenging the diabetes community to effectively communicate the vast amount of new information to the scientific community, primary care practitioners, and the public. Federal funding of the work of dedicated scientists, and the cooperative initiatives of the National Institutes of Health, the National Diabetes Advisory Board, the American Diabetes Association, and the Juvenile Diabetes Foundation are contributing both to our understanding of diabetes and how to treat it and to the communication of this information to those who can employ and benefit from it. Much remains to be learned, but if the past few years are any indication, the coming decade holds great promise.

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